REMARKS

STATUS OF THE CLAIMS.

Claims 2-6, 9-15, 18-20, 23, 25, 26, 43, 44, and 46-48 are pending with entry of this amendment, claims 46 and 47 being added. All previously pending claims have been converted from product-by-process claims to method claims. Independent claim 23 has been further amended to even more clearly recite the invention. New dependent method claim 46 finds support throughout the specification and in Examples 1-3. (See, e.g., figure descriptions for Figures 15 and 16, which we present in Appendix A, as filed, and inserted into the body of the specification in the Amendment dated June 1, 2004). New claims 47 and 48 are product-by-process claims relating to the methods of claims 23 and 46, respectively. Thus, these amendments introduce no new matter.

35 U.S.C. §103.

Black, Fransson, and Montesano

Claims 2-6, 9-15, 18-20, 23, 25, 26, 43, and 44 were rejected under § 103(a) as unpatentable over Black et al. (1998, FASEB J. 12, 1331-1340), in view of Fransson et al. (British Journal of Dermatology (1998) 139:59-64) and Montesano (1983, J. Cell Biol., 97, 1648-52). Office Action, page 2. The rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate that (1) all elements of the invention are found in the cited art; (2) the cited art provided motivation to combine or, if necessary, modify these elements to arrive at the claimed invention; and (3) the cited art revealed that, in making the claimed invention, those of ordinary skill in the art would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Claims 2-6, 9-15, 18-20, 23, 25, 26, 43, 44, and 46

Of the rejected claims, only claim 23 is independent. Claim 23 recites:

> A method of producing an artificial tissue, said method comprising: mixing together a support matrix and connective tissue cells to form a support matrix-connective tissue mixture and forming an original culture comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells, wherein said endothelial cells contact inner surfaces of the support matrix-connective tissue mixture layers, and wherein the cells are from the

same species, whereby said original culture produces an artificial tissue comprising one or more microvessels and one or more mononuclear leukocytes.

The Examiner states that "Black et al. teach a skin equivalent preparation comprising human keratinocytes plated on endothelial dermal equivalent or endothelial fibroblast dermal equivalent mixed with collagen (see page 1333, 1st col., 2nd and 3rd paragraph)." Office Action, page 2. This statement is incorrect. Black fails to teach or suggest ***mixing*** any cell type with collagen. In particular, in the cited passages, Black teaches seeding (1) fibroblasts ***on top*** of a chitosan/collagen biopolymer; (2) endothelial cells ***on top*** of the biopolymer; and (3) a mixture of fibroblasts and endothelial cells ***on top*** of the biopolymer. Keratinocytes (epithelial cells) were then plated on top of all three culture types. Thus, Black fails to teach or suggest "mixing together a support matrix and connective tissue cells to form a support matrix-connective tissue mixture," as recited in claim 23.

As the Examiner recognizes, Black also fails to teach or suggest "forming an original culture comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells." For this aspect of claim 23, the Examiner cites Montesano. Office Action, page 3. Montesano teaches cultures containing "endothelial cells grown inside a three-dimensional collagen matrix." Montesano, abstract. Montesano describes two different variations of these cultures, produced by "(a) resuspending freshly trypsinized cells in gelling collagen solutions ***or*** (b) allowing endothelial cells to attach to the surface of a collagen gel and covering them with a second collagen layer before the occurrence of cell spreading." Nothing in Montesano teaches or suggests mixing a collagen solution with an entirely different cell type, namely connective tissue cells, such as fibroblasts. To the contrary, Black teaches that fibroblasts should be cultured on top of the support matrix. Moreover, neither Black nor Montesano provides any motivation for, in effect, combining what Montesano presents as alternative embodiments; i.e., cells are ***either*** mixed into collagen gels ***or*** sandwiched between them, not both, as recited in claim 23.

The Examiner recognizes that the Montesano-Black combination is also deficient in failing to teach that "said original culture produces an artificial tissue comprising one or more . . . mononuclear leukocytes." The Examiner cites Fransson for this teaching. Office Action, page 3. Fransson describes cultures quite different from the simple, defined systems described in Black and Montesano. In particular, Fransson teaches "inserting skin biopsies . . . into dermal equivalents."

The Examiner has provided no rationale for why one of skill in the art would extrapolate any findings from such a culture to cultures consisting of one to three cell types and a support matrix. Accordingly, the record is devoid of any reason why one skilled in the art would believe that the presence of mononuclear leukocytes in a skin biopsy culture says anything about the ability of defined cultures of Black or Montesano to produce mononuclear leukocytes. Indeed, the dendritic cells on which the Examiner relies were present in "epidermal outgrowths" from the skin biopsies. See, e.g., Fransson, page 602, col. 2. That a cell type present in a biopsy is present in an outgrowth from that biopsy says nothing about the ability of the Black and Montesano cultures to produce a cell type that is not present in the original culture. Applicants respectfully submit that the method of Fransson is simply too different from the methods described by Black and Montesano to teach or suggest anything about whether such cultures could produce mononuclear leukocytes

Moreover, Black and Montesano were concerned *inter alia* with producing systems useful for studying angiogenesis in vitro. Fransson was concerned with culturing Langerhans cells for the purpose of studying contact allergic reactions. The record is devoid of any motivation for combining Fransson with Black and/or Montesano. Given the completely different natures of these systems, i.e., biopsies versus defined systems with one to three cell types, it is completely unclear how one skilled in the art would combine the teachings of Fransson with those of Black and/or Montesano.

It is well-settled that a *prima facie* case requires ***specific*** motivation to produce the invention. The Federal Circuit emphasized the necessity for finding specific motivation in *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). There, the court stated:

> "[V]irtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698, 218 U.S.P.Q. 865, 870 (Fed. Cir. 1983)*; *see also Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 U.S. P.Q. 8, 12 (Fed. Cir. 1983)* ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *Sensonics,*

> *Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q. 2d 1551, 1554 (Fed. Cir. 1996).*

Id. at 1357. The court then noted that the Board had failed to "explain what ***specific*** understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested" the invention. *Id.* (emphasis added). In *In Re Werner Kotzab*, 217 F.3d 1365 (Fed. Cir. 2000), the Federal Circuit reiterated that:

> [A] rejection cannot be predicated on the mere identification in . . . [the cited reference] of individual components of claimed limitations. Rather, ***particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.***

In re Kotzab, at 1369-1372 (emphasis added). As such findings have not been made in the present case, Applicants respectfully submit that Fransson cannot be relied upon to support a *prima facie* case of obviousness.

Accordingly, Fransson cannot remedy any of the deficiencies of the Black-Montesano combination. To summarize, this combination fails to teach or suggest: (1) "***mixing*** together a support matrix and connective tissue cells to form a support matrix-connective tissue mixture," (2) ***and*** forming a "sandwich"-style "culture comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells" (Montesano teaches either mixing ***or*** forming a sandwich-style culture), and (3) that the resulting culture "produces an artificial tissue comprising one or more . . . ***mononuclear leukocytes***." Because the cited combination fails to teach or suggest these elements of claim 23, this claim is patentable over the cited combination.

Claims 2-6, 9-15, 18-20, 25, 26, 43, 44, and 46 are patentable over the cited combination at least by virtue of their dependence, directly or indirectly, from claim 23. In addition, dependent claim 46 recites the "method of claims 2 or 23 wherein . . . mononuclear leukocytes are not present in the original culture, but are formed during culturing." The Examiner relies on Fransson's disclosures regarding dendritic cells for the teaching of mononuclear leukocytes. However Fransson teaches:

> In this model, the keratinocytes as well as the LCs ***migrated out*** from a skin biopsy implanted in the centre of a dermal equivalent consisting of fibroblasts in a collagen lattice. . . . The epidermal outgrowths were readily populated by dendritic cells, identified as LCs by staining with antibodies . . . .

Fransson, page 602, paragraph bridging cols. 1-2. This passage makes it clear that dendritic cells (LCs) were present in the original culture and migrated out from the skin biopsy into the collagen lattice, which teaches away from claim 46. Fransson, in effect, demonstates the persistence of a cell type in a culture, whereas the claim 46 relates to the production of a ***new*** cell type in a culture. Claim 46 is thus free of the § 103 rejection for this additional reason.

In view of the foregoing, claims 2-6, 9-15, 18-20, 23, 25, 26, 43, 44, and 46-49 clearly patentable over Black in view of Fransson and Montesano. Withdrawal of the § 103 rejection is therefore respectfully requested.

Claims 47 and 48

Claim 47 recites a "artificial tissue produced by the method of claim 23." As explained above, the Black-Montesano combination fails to teach or suggest an artificial tissue produced (1) "***mixing*** together a support matrix and connective tissue cells to form a support matrix-connective tissue mixture" ***and*** (2) forming a sandwich-style "culture comprising two layers of support matrix-connective tissue mixture separated by a layer of endothelial cells." Combining Black and Montesano as the Examiner has done would, at best, yield a culture in which connective tissue and endothelial cells are layered on top of a support matrix, as taught in Black, and then overlaid with another layer of support matrix, as taught in Montesano. However, this is not the culture recited in claim 47, which requires that the connective tissue cells be mixed into the support matrix.

The Black-Montesano combination also fails to teach or suggest that the resulting culture "produces an artificial tissue comprising one or more . . . ***mononuclear leukocytes***." As explained above, Fransson cannot be relied upon for this teaching because Fransson relates to a substantially different system (including skin biopsies) than the defined systems of Black and Montesano, and the record contains no motivation for combining these systems, no guidance as to how they should be combined (except in Applicants' specification), and no reasonable expectation as to the results of this combination. For these reasons, claim 47 is free of the § 103 rejection over Black in view of Fransson and Montesano.

Claim 48 recites a "artificial tissue produced by the method of claim 46." Claim 46 depends ultimately from claim 23. Accordingly, claim 48 is patentable over Black in view of Fransson and Montesano for the same reasons as claim 47.

CONCLUSION.

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

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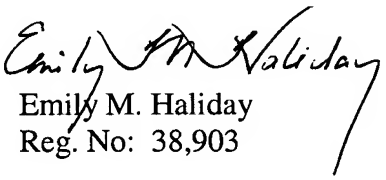
Respectfully submitted,



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